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TITLE: Ambulatory and Non-Ambulatory Benefits of Lower Limb Exoskeleton Use, with and without FES, in Clinical and Community Settings

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14. ABSTRACT

This research investigates the extent to which regular walking in an exoskeleton will provide mobility, health, and recovery benefits to individuals with spinal cord injury. The research is comprised of three sub-studies. The first investigates prospective benefits while walking in an exoskeleton; the second investigates prospective additional benefits when the exoskeleton is supplement with lower limb functional electrical stimulation; and the third investigates prospective benefits during home and community use. As of this first annual report, the first study is underway, with two of 24 subjects enrolled. Although all sites have received exoskeleton training and IRB approval, only the Mayo Clinic has received HRPO approval. HRPO review has taken much longer than expected, in part due to an unexpected change in the Human Subjects Protections Scientist at HRPO assigned to review the study.

15. SUBJECT TERMS
spinal cord injury, paraplegia, exoskeleton, physical medicine and rehabilitation, rehabilitation research, legged mobility, neuromuscular impairment, neural and functional recovery

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TABLE OF CONTENTS

1. INTRODUCTION

This research investigates the extent to which regular walking in an exoskeleton will provide mobility, health, and recovery benefits to individuals with spinal cord injury. The research is comprised of three sub-studies. The first investigates prospective benefits while walking in an exoskeleton; the second investigates prospective additional benefits when the exoskeleton is supplement with lower limb functional electrical stimulation; and the third investigates prospective benefits during home and community use. The respective studies will characterize effects of exoskeleton walking on pain, spasticity, bowel and bladder function, body-mass index (BMI), bone mineral density (BMD), cardiovascular health, well-being, potential neurological recovery, and level of mobility. The research is being conducted at three sites – Vanderbilt Medical Center, Mayo Clinic, and the Tampa VA – each of which is conducting the same study protocol. The first two studies, each of which are conducted in a clinical setting, will enroll 24 subjects total (8 per study site), while the third, which is a take-home study, will enroll 6 subjects total (2 per study site). The first study is expected to be completed by 12/30/2017; the second by 03/30/2019; and the third by 09/30/2019.

2. KEYWORDS

- spinal cord injury
- paraplegia
- exoskeleton
- physical medicine and rehabilitation
- rehabilitation research
- legged mobility
- neuromuscular impairment
- neural and functional recovery

3. ACCOMPLISHMENTS

3.1. What were the major goals and objectives of the project?

As mentioned in the introduction, this research entails three sub-studies. The major goal of the first year was to approve and initiate the study 1 protocol at all study sites. The intent of study 1 is to determine the extent to which regular walking in an exoskeleton provides health benefits, functional or neurological recovery, and legged mobility to non-ambulatory or poorly-ambulatory individuals with SCI. Study 1 is expected to enroll 24 subjects, 8 at each study site. Each subject is expected to be involved in the study for 2 months of active intervention (i.e., walking with the exoskeleton), with an additional follow-up measurement of outcomes 2 months later. As per the SOW, study 1 was expected to begin enrolling subjects 04/01/2016, and to complete the protocol on all 24 subjects by 12/30/2017.

The tasks and subtasks associated with approving and initiating study 1 protocol, along with the status of each, along with the start and end dates as given in the

SOW, are as follows:

- Major task 1: Finalize protocol and obtain IRB/HRPO approval
    - Target state date: 09/30/2015
    - Target completion date: 03/30/2016
    - Status: Task is overdue.
    - Detailed status:
        - IRB approval: All sites have final IRB approval.
        - HRPO approval:
            - Mayo has final HRPO approval and has begun the study.
            - Vanderbilt is awaiting final HRPO approval (application submitted 4/13/2016)
            - Tampa VA is awaiting HRPO approval (application submitted 9/15/2016)
    - Subtasks and status of each:
        - Subtask 1: Refine eligibility criteria, exclusion criteria, screening protocol (status: completed)
        - Subtask 2: Finalize outcome measures and assessment procedures (status: completed)
        - Subtask 3: Finalize consent form and human subjects study protocol (status: completed)
        - Subtask 4: Coordinate with sites for IRB protocol submission (status: completed)
        - Subtask 5: Coordinate with sites for IRB/HRPO review (status: continuing)

- Major task 2: Conduct study 1
    - Target start date: 04/01/2016
    - Target completion date: 12/30/2017
    - Status: Study is underway at Mayo. All sites have been trained to use the exoskeletons, and Mayo has enrolled their first two subjects and has completed the first several weeks of protocol with them.
    - Subtasks and status of each:
        - Subtask 1: Coordinate with sites for delivery of exoskeletons and training of clinical staff (status: completed)
        - Subtask 2: Enrollment of subjects (status: underway)
            - Detailed status:
                - Mayo has enrolled first two subjects.
                - Vanderbilt and Tampa have each unofficially enlisted first two subjects, but are waiting on HRPO approval to officially enroll.
        - Subtask 3: Conduct exoskeleton walking protocol (status: underway)
            - Detailed status:
                - Mayo has begun conducting walking protocol with first two subjects.

        - Vanderbilt and Tampa awaiting HRPO approval to proceed.
        - Subject-specific study protocol notebooks and record books have been assembled with session-by-session instructions and data entry.
        - Electronic data entry forms have been established in REDCap.
    - Subtask 4: DXA scans (distal femur, proximal tibia) at baseline, end of treatment, and 8-week post-treatment follow-up (status: protocol finalized and underway).
    - Subtask 5: Health, neurological, and functional outcome measures at baseline, mid-point (4 weeks), end of treatment (8 weeks), and 8-week post-treatment follow-up (status: underway at Mayo, awaiting HRPO approval to initiate at Vanderbilt and Tampa).
    - Subtask 6: Conduct analysis of data from Study 1 (status: not started).

3.2. What was accomplished under these goals?

- Major activities:
    - Completed subcontracts between assessment sites.
    - Completed conflict of interest and management plan review at Vanderbilt.
    - Reviewed and finalized study 1 protocol, including study procedures, inclusion criteria, outcome measures.
    - Finalized assessment instruments, including self-report survey and DEXA protocol.
    - Finalized informed consent documents.
    - Obtained final IRB approval at all three study sites.
    - Completed and submitted HRPO application for all three study sites.
    - Completed purchase and delivery of all exoskeletons to all study sites.
    - Completed exoskeleton training at all study sites.
    - Initiated lists of potential subjects at each respective assessment site.
    - Assembled protocol and documentation notebooks for use with each subject.
    - Established REDCap database for multisite data entry.
    - Obtained final HRPO approval for Mayo.
    - Enrolled first two subjects and initiated study protocol at Mayo.

- Specific objectives:
    - Prepare protocol for study 1.
    - Obtain all approvals necessary to begin conduct of study 1.
    - Begin conduct of study 1.

- Significant results or key outcomes:
    - Obtained IRB approvals at all sites.

- Submitted for HRPO approval April 2016
- Obtained HRPO approval for one study site (Mayo Clinic)
- Enrolled two subjects and initiated study at Mayo Clinic

- Other achievements: None yet.

3.3. What opportunities for training and professional development did the project provide?

Clinical staff at all study sites attended a 3-day course and obtained training and certification to use exoskeletons in clinical practice.

3.4. How were the results disseminated to communities of interest?

No results yet to disseminate.

3.5. What do you plan to do during the next reporting period to accomplish the goals and objectives?

My highest priority is to obtain HRPO approval at Vanderbilt and Tampa, so all three sites will be able to enroll subjects and conduct the protocol. Mayo is underway with the protocol, and both Vanderbilt and Tampa are fully ready to start, including having subjects lined up to start (although of course not yet enrolled). Once all sites have approval, the forward progress of the study will largely take care of itself.

4. IMPACT

4.1. What was the impact on the development of the principal discipline(s) of the project?

Nothing to report.

4.2. What was the impact on other disciplines?

Nothing to report.

4.3. What was the impact on technology transfer?

Nothing to report.

4.4. What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS

5.1. Changes in approach and reasons for change

None to report.

5.2. Actual or anticipated problems or delays and actions or plans to resolve them

The Mayo Clinic is enrolling subjects, and will shortly enroll its second set of subjects. The other two sites are ready to start the study, but there has been an unanticipated delay in HRPO approvals. The Vanderbilt HRPO application was submitted concurrently with the Mayo application, both by the Vanderbilt study coordinator, and both with the same protocol. Mayo received HRPO approval in early August, but Vanderbilt has been awaiting approval for eight months. Apparently, the delay has been due to two issues. Firstly, due to a determination by the Vanderbilt IRB that it may have an institutional conflict of interest, it subcontracted all IRB review to the University of Alabama Birmingham (UAB) IRB, which added an additional layer of communication to the process. Secondly, the Human Subjects Protections Scientist that was reviewing the case at HRPO left, apparently suddenly and unexpectedly. Review of the study has been transferred to a new Human Subjects Protections Scientist, but without a transfer of case documents. In any case, the study is now under review at HRPO. It is my highest priority at this point to assist in any way I can to facilitate the review, so that we can start conducting the study protocol at the Vanderbilt and Tampa sites.

Despite the unanticipated delays in approval, all other aspects of the study are proceeding as expected. My plan is to recover the original project schedule by the end of study 1 by enrolling three subjects concurrently in the second and third enrolled groups (i.e., 2+3+3) rather than two subjects at a time (i.e., 2+2+2+2), but we will not pursue that strategy until all sites have completed the first two subjects.

5.3. Changes that had a significant impact on expenditures

The above noted delay in obtaining HRPO approval has reduced the rate of anticipated expenditure. However, the purchase of exoskeleton kits for the study sites was supposed to have been conducted according to a payment schedule. Due to an error in the Vanderbilt purchasing office, the exoskeleton kits were purchased in a single lump-sum payment. I alerted the purchasing office to this error, but I have not followed up to see whether or not they resolved the issue (which would have entailed a refund from the manufacturer). Therefore, the delay in study expenses due to the delay in approval is at this point offset by the unexpected additional expense of lump-sum payment for the exoskeletons.

5.4. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

None to report.

6. PRODUCTS

Nothing to report.

7. PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS

7.1. What individuals have worked on the project?

Name: Dr. Michael Goldfarb
Project Role: PI, Vanderbilt lead researcher
Researcher Identifier: ORCID ID 0000-0002-6622-095X
Nearest person month worked: 3
Contribution to Project: Dr. Goldfarb is coordinating the research effort.

Name: Ms. Sheri Dixon
Project Role: Vanderbilt study coordinator
Researcher Identifier: n/a
Nearest person month worked: 2
Contribution to Project: Ms. Dixon is the Vanderbilt study coordinator, has been assembling IRB and HRPO applications for Vanderbilt and all sites, has set up the REDCap database, and the overall project (i.e., multi-site) study coordinator.

Name: Ms. Christina Durrough
Project Role: Vanderbilt lead physical therapist
Researcher Identifier: n/a
Nearest person month worked: 1.5
Contribution to Project: Ms. Durrough has been assisting with design and assembly of the protocol and data recording notebooks, and is responsible for exoskeleton use and oversight.

Name: Dr. Kristin Zhao
Project Role: Mayo lead researcher
Researcher Identifier: ORCID ID 0000-0001-7598-8197
Nearest person month worked: 2
Contribution to Project: Dr. Zhao is leading the research effort at the Mayo Clinic.

Name: Ms. Megan Gill
Project Role: Mayo Clinic lead physical therapist
Researcher Identifier: n/a
Nearest person month worked: 1.25

Contribution to Project: Ms. Gill has been administering the study protocol on the two subject currently enrolled at Mayo.

Name: Mr. Tyson Scrabeck
Project Role: Mayo study coordinator
Researcher Identifier: n/a
Nearest person month worked: 1
Contribution to Project: Mr. Scrabeck has authored and assembled IRB and HRPO applications for the Mayo site.

Name: Dr. Sam Phillips
Project Role: Tampa VA lead researcher
Researcher Identifier: n/a
Nearest person month worked: 2
Contribution to Project: Dr. Phillips leading the research effort at the Tampa VA.

Name: Mrs. Padmaja Ramaiah
Project Role: Tampa VA study coordinator
Researcher Identifier: n/a
Nearest person month worked: 1
Contribution to Project: Mrs. Ramaiah has authored and assembled IRB and HRPO applications for the Tampa site.

7.2. Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report.

7.3. What other organizations were involved as partners?

Organization Name: Mayo Clinic
Location of Organization: Rochester MN
Partner's contribution to the project (identify one or more)

- Collaboration: Mayo is one of the three study sites conducting the study protocol.

Organization Name: Tampa VA
Location of Organization: Tampa Bay FL
Partner's contribution to the project (identify one or more)

- Collaboration: Tampa is one of the three study sites conducting the study protocol.

8. SPECIAL REPORTING REQUIREMENTS: Included in Appendix.

9. APPENDICES: Quad chart included on next page.

Ambulatory and Non-Ambulatory Benefits of Lower Limb Exoskeleton Use, with and without FES, in Clinical and Community Settings

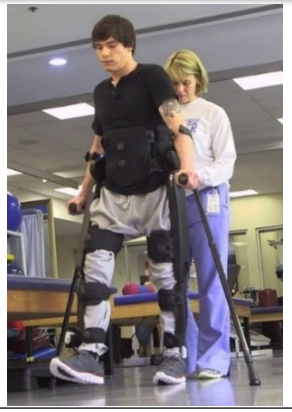
Log no. SC140121

Award no. W81XWH-15-2-006

PI: Michael Goldfarb **Org:** Vanderbilt University **Award Amount:** $2,344,016

Study Aims

- Study 1: Determine extent to which regular walking in an exoskeleton provides health benefits, functional or neurological recovery, and legged mobility to non-ambulatory or poorly-ambulatory individuals with SCI.
- Study 2: Determine extent to which regular exoskeletal walking, when supplemented with functional electrical stimulation (FES) of leg and trunk muscle groups, will result in enhanced therapeutic and neurological benefits relative to exoskeleton use without FES.
- Study 3: Determine extent to which regular use of an exoskeleton in the home and community will result in enhanced therapeutic and neurological benefits relative to exoskeleton use in a clinic, to determine the extent to which the level of mobility provided by the exoskeleton will be amenable to home and community use, and to characterize the level of compliance of exoskeleton use.



SCI subject walking with exoskeleton. The subject is shown for illustrative purposes only, and is not part of the proposed study.

Accomplishments and status: Study 1 underway; obtained IRB approvals from all sites; completed exoskeleton delivery and training at all sites; obtained HRPO approval for Mayo; awaiting HRPO approval at Vanderbilt and Tampa; first two subjects enrolled and undergoing study at Mayo; Vanderbilt and Tampa ready to begin study pending HRPO approval.

Timeline and Cost

Budget Year	15/16	16/17	17/18	18/19
Activity/Dates	09/30/15-09/29/16	09/30/16-09/29/17	09/30/17-09/29/18	09/30/18-09/29/19
IRB/HRPO				
Enrollment				
Study 1				
Study 2				
Study 3				
Publication				
Estimated budget ($k)	$597	$578	$593	$581

Updated: 12/03/2016

BY15/16 Goals

- ✓ Study 1 underway
- ❑ 8 subjects complete

BY16/17 Goals

- ❑ Study 1 completed
- ❑ IRB/HRPO approval for Study 2

BY17/18 Goals

- ❑ Study 2 underway and 80% complete (~18 subjects complete)
- ❑ Study 3 IRB/HRPO review initiated

BY18/19 Goals

- ❑ Study 2 complete
- ❑ Study 3 complete

Comments/Challenges/Issues/Concerns

Study 1 is underway at Mayo, but still awaiting HRPO approval at Vanderbilt and Tampa. Project is currently behind schedule due to delays in approval process, but is expected to recover original schedule by end of Study 1.

Budget Expenditure to Date

Projected Expenditure: $597k (assuming even burn rate through BY)

Actual Expenditure: $771k (reflects full cost of all exoskeleton kits; Vanderbilt was supposed to purchase in payments, but instead paid in full, and have not yet corrected the error).